

Introduction

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Medical genetics is infinitely complex. The good news is that for the basic sciences in a field where the provider is NOT a geneticist, the need-to-knows are actually quite slim. We've chosen to hit the highest of the high-yield. It's an exciting time for genetics—diagnostics, screens, and treatments. The methods are complex and the procedures specialized. But, much like delivering a strangulated fetus or suturing a heart valve into place—the new student in the basic sciences only needs to know it at a basic level. This short course highlights the most important information.

This first lesson is an overview, vocabulary builder, and warmup to the course. The material is familiar from the MCAT and treated in greater detail there than needed here. But review and internalize everything in this lesson anyway, because each subsequent lesson assumes and requires a mastery of this content.

Genetic Complement

All human cells (except gametes) have **two copies of each chromosome**. That means we're **diploid**. At any given time, somatic cells have "**2n**" DNA—two copies of everything. One copy comes from dad's gamete (the sperm) and one copy comes from mom's gamete (the egg). There are **23 chromosomes**—the **22 autosomes** and **1 sex chromosome**. And because we have two copies of each chromosome, there are a total of 46 chromosomes in each cell. Gametes are **haploid** and have only half the genetic complement of somatic cells, so have "**1n**" DNA, only one copy of each, for a total of 23 chromosomes.

Humans should have two copies of each chromosome. That is, when we as providers look through a microscope and assess chromosome 1, we should see **two copies** of chromosome 1. A **chromosome** is a **continuous piece of DNA** connected by a **centromere**. Be careful with the nomenclature and the genetic component for this next part.

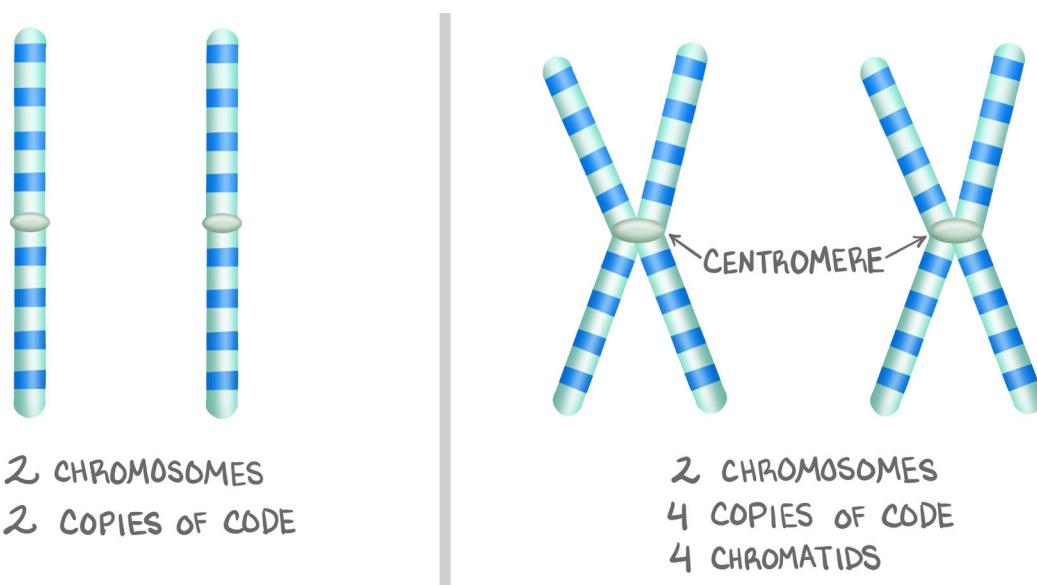


Figure 1.1: Chromosomes and Chromatids

The colored regions represent the “original chromosome.” When joined together by a centromere, no matter how many copies of the genetic material there are within the butterfly-shaped structure, it’s one chromosome. The colored portion in the butterfly chromosome is then called one chromatid, part of the chromosome. Chromatids exist only as part of chromosomes.

Sister Homologous Chromosomes are the two copies of the one chromosome that exist in every cell, one from mom and one from dad. We have two copies of chromosome 1. They're homologous to each other. During replication the DNA is copied. Both sister homologous chromosomes are copied. At this point, there are **still two homologous chromosomes**, even though the amount of DNA has doubled. Whereas before replication there were two sister homologous chromosomes, each with one chromatid, after replication there are still two sister homologous chromosomes, but each with two chromatids. A **chromatid** is a chromosome-attached-at-the-centromere. When the chromatids are pulled apart in cell division, we call them chromosomes—the chromatid will eventually be a chromosome if separated from its partner.

The genetic code is reliably repeated in humans. A **gene** is the inheritable unit of the genetic code. It contains the genetic code that allows for both regulation of that gene and for expression of the gene. The gene is the nucleotide sequence that can eventually become protein (not all genes code for proteins, but genes that make protein are the subject of medical genetics that we care about in this course). Genes exist at specific locations on chromosomes, called **loci**. All humans should have the same gene at the same locus. Loci allow us to visually inspect the chromosome, anticipating where a gene (or mutation) might be.

An **allele** is a **variation of a gene**. The two alleles code for the same protein, but the proteins are different from each other. The variation in the gene exists between sister homologs. One gene variant comes from dad and one from mom. In medical genetics, we're going to assume, for almost all diseases, there are only two possible variants of a gene, a good one and a bad one.

The combination of two alleles gives the **genotype**. The genotype is the **final genetic code**—the DNA sequence only. **Homozygous** means **both alleles are the same**. **Heterozygous** means there are two different alleles. It doesn't necessarily tell us what's going to happen to the patient, only what the DNA sequence is. The genotype can inform the phenotype but doesn't strictly determine what the patient experiences. The **phenotype** is what the **patient experiences**—the signs, symptoms, or characteristics caused by the genotype.

Mutations cause variations of genes, leading to disease states. A **dominant allele** is one in which if a **single bad copy** is present, the disease will be expressed. This is usually a **gain-of-function** mutation. **Recessive alleles** require that **both copies be lost** for disease to be expressed. Because there are two copies of every gene, and often one copy can accommodate the absence of its partner, often, **recessive alleles are the source of loss-of-function** mutations.

Cell Cycle

Covered briefly here, as it's discussed in more detail in the Inflammation and Cancer sections.

G1 has **two chromosomes**, each with one chromatid. Diploid ($2n$) genetic complement. G1 can express proteins, transcribe, and translate genes.

Synthesis (S phase) is the period of DNA replication. All the DNA is replicated. All the " $2n$ " data is copied, meaning there is " $4n$ " worth of DNA in the cell. Sister chromatids are still attached to each other and sister chromosomes align to be separated.

G2 has **two chromosomes**, each with **two chromatids**. These cells technically have $4n$ genetic material in their genetic complement. However, they still have only 46 chromosomes (they have 92 chromatids). Like G1, G2 can express proteins, transcribe, and translate genes.

Mitosis (M phase) is when the cell actually pulls the chromosomes apart from one another, allowing for cell division.

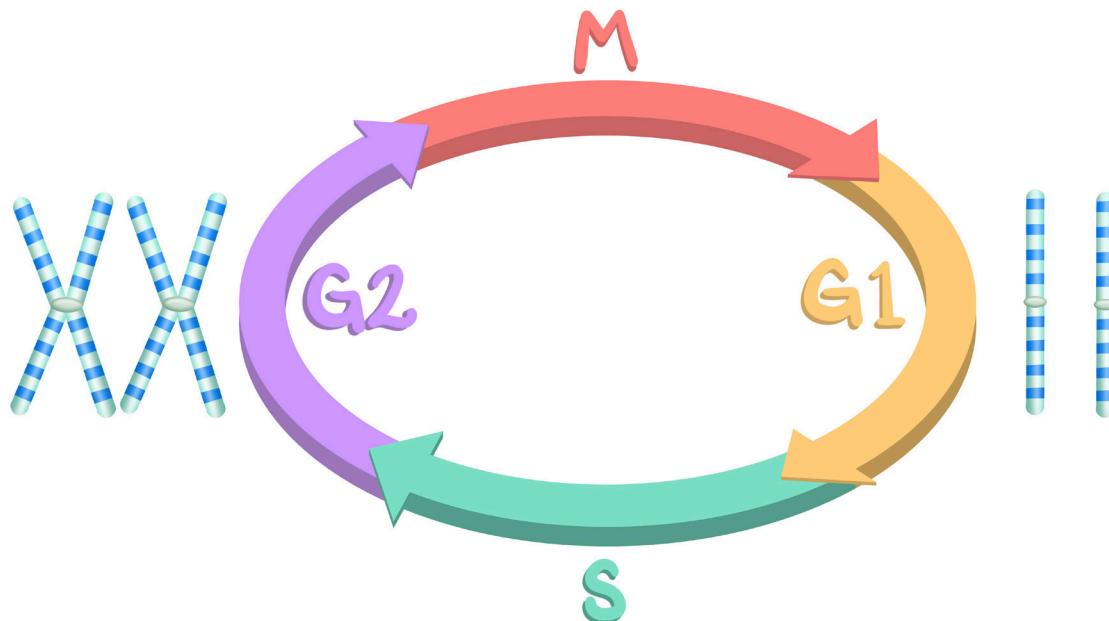


Figure 1.2: Cell Cycle Simplified

There are four phases of the cell cycle: G1 where there are 2 copies of every gene on 2 chromosomes, a synthesis phase that copies the genetic code, a G2 phase where there are 4 copies of every gene on 2 chromosomes, and a mitosis phase where the cell divides into two daughter cells.

Karyotyping

Karyotyping describes the number and appearance of chromosomes in their most condensed form, often evaluated during mitosis under a light microscope. A karyotype is a complete set of an organism's chromosomes. Sometimes karyotypes are displayed with sister homologous chromosomes (two for every chromosome), and sometimes without (one for every chromosome). Sometimes it's the beginning of metaphase chromosomes (the butterfly) and sometimes it's the end of metaphase (singular strand).

By karyotype, we describe the **size**, **centricity**, and **arms**. The **q-arm** is the **long one**, while the **p-arm** is the short one. Chromosomes are organized by size. Chromosome 1 is the largest, and chromosome 22 is the smallest. The 23rd chromosome is the sex chromosome.

If the two arms are equal, it's termed **metacentric**. If one arm is longer than the other, it's termed **sub-metacentric**. If only the telomeres exist above the centromere, it's termed **acrocentric**. Only acrocentric chromosomes can undergo Robertsonian translocation.

If a **Y is present**, the patient is genetically male. If there's no Y, **female is the sex default**. Even with a Y (genotype) there's not necessarily the expression of male features (phenotype). The Y chromosome has several genes on it that make proteins that do things for that to happen.

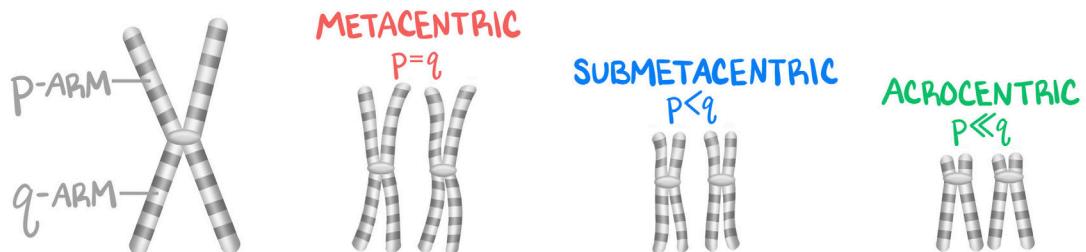
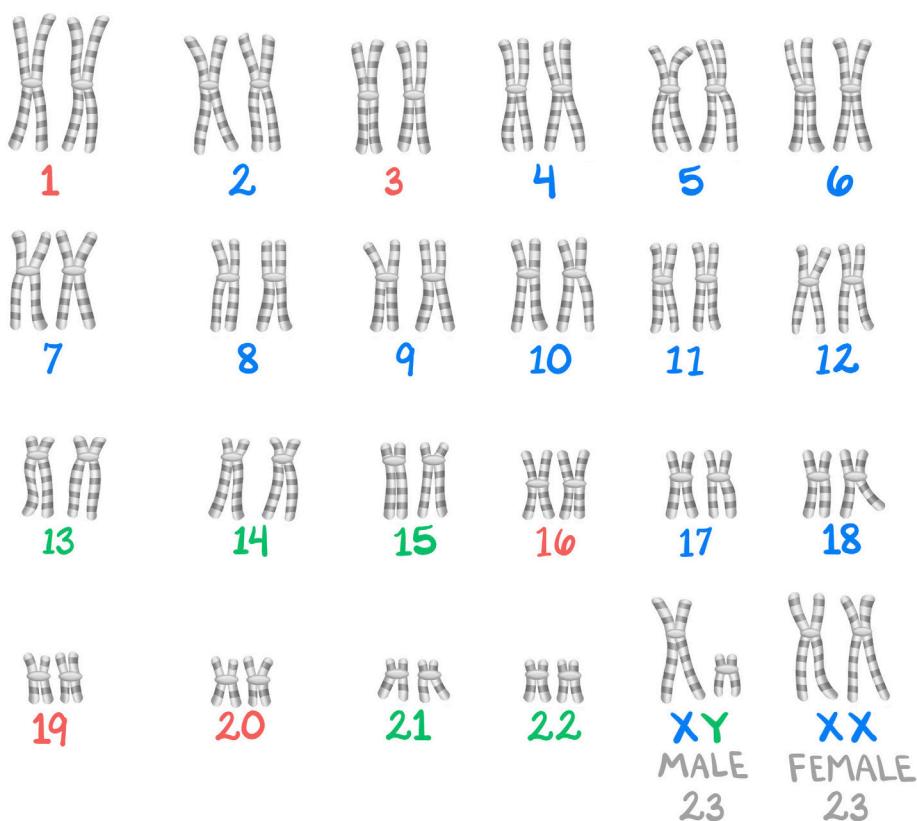


Figure 1.3: Karyotyping

Meiosis

Meiosis is the formation of gametes, **haploid cells**. Sister chromatides, each containing sister chromatids, line up in the middle. The two chromosomes are pulled apart from each other. **Meiosis I** is the separation of the **sister chromatides** from each other. In **meiosis II**, sister **chromatids** are pulled apart from each other. In the end, **four cells are made**, each with only “ $1n$ ” genetic material.

In S phase, the cell goes from $2n$ to $4n$. In meiosis I, the cell goes from one cell with $4n$ to two cells with $2n$ each. In meiosis II, the two cells with $2n$ each because four cells with $1n$ each.

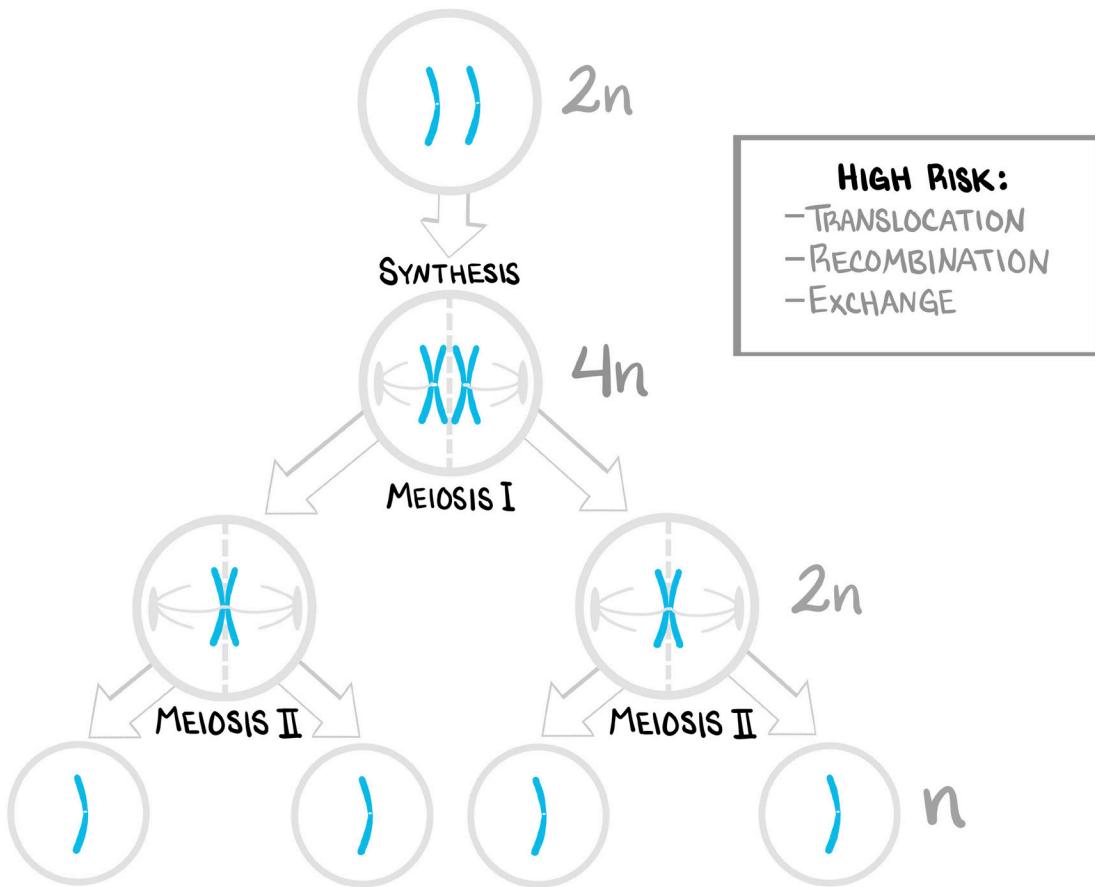


Figure 1.4: Meiosis I and II

In meiosis I, homologous chromosomes line up next to each other, so that each chromosome, consisting of two chromatids, is separated from its homolog. This is the difference from mitosis, where homologs do not line up next to each other, but all join the same metaphase plate. Meiosis II then forms gametes from the resultant one chromosome with two chromatids, separating the chromatids, forming a gamete. Translocation or recombination has its highest risk in meiosis because of the side-by-side alignment of homologs not present in mitosis.